# HuGE Fact Sheet

## IL2RG and Severe Combined Immunodeficiency (SCID), a Primary Immunodeficiency Disease (PID)

Rovshan Ismailov, MD, MPH (University of Pittsburgh)

PUBLISHED: July 2002

**IL2RG Gene**

The *IL2RG* gene, located at Xq13, encodes the gc-chain of the IL2, 4, 7, 9, and 15 cytokine receptors that are essential for the development of T and NK lymphocyte subsets. Mutations in the *IL2RG* gene cause the X-linked form of Severe Combined Immunodeficiency Disorder (SCID), a subset of the PID disorders.

**Prevalence Of Gene Variants**

A total of 264 mutations of the *IL2RG* gene have been sequenced, of which 169 are unique (8). Each of these mutations has resulted in gc deficiency with varying degrees of immune deficiency (5). The penetrance of each of the identified *IL2RG* mutations is unknown. The mutations are distributed throughout the eight exons of the gene, as well as in the regions necessary for proper transcription and translation. Exons 5 and 7 have mutation hot spots. The types of mutations identified include missense, nonsense, insertions, deletions, splice mutations, and mutations that affect RNA processing and translation. No population based data exists to describe the frequency of mutations in *IL2RG*.

**Disease Burden**

SCID, an inevitably fatal form of PID that presents in infancy, is caused by mutations in a number of genes, including the *IL2RG* gene. In two clinical series, patients with mutations in *IL2RG* represent 28% to 45% of all SCID cases (5,6). The estimated incidence of SCID is 1:100,000 live births. SCID resulting from mutations in IL2RG (XSCID) is characterized by profound deficiencies of T and NK cells but normal to elevated levels of B cells. These patients usually present as infants, often with diarrhea and failure to thrive. They also are susceptible to severe and often fatal infections with organisms such as *Candida albicans*; *Pneumocystis carinii*; *Pseudomonas*; and *Salmonella* species, as well as viruses such as respiratory syncytial virus and herpes viruses (5). Infants with SCID have undetectable tonsils and usually undetectable peripheral lymph nodes. The thymus gland is small and poorly differentiated (5). On rare occasions, mutations in IL2RG have caused an atypical mild combined immunodeficiency that presented beyond infancy (5).

Successful treatment of XSCID involves immune reconstitution by transplantation of either HLA-identical unfractionated bone marrow or haploidentical T-cell-depleted bone marrow. Bone marrow transplantation is also the treatment of choice for SCID caused by mutations in other genes. Transplantation is more successful if done early in infancy, before the onset of life threatening infections. In a series from one clinical center, infants who received transplants in the first three and a half months had a 95% survival rate while infants receiving transplants after three and a half months had a survival rate of 76% (1). Post-transplant recipients may require ongoing immunoglobulin replacement and antibiotics.

Recently, gene therapy as a treatment for XSCID has been tested in five patients at another clinical center (3). Autologous CD34 + bone marrow cells were transduced ex vivo with a replication incompetent retroviral vector containing a gene encoding a normal gc-chain. Initial results (two and a half years post-treatment) in four patients indicate that they have nearly normal T-cell numbers and phenotypes. These T cells also had nearly normal repertoires of T-cell

receptors and in vitro proliferative responses to antigens. Although the frequency of transduced B cells was low, these children did not require immunoglobulin replacement (3). One patient underwent stem-cell transplantation eight months after gene therapy due to the failure of T-cell reconstitution (3).

**Laboratory Tests**

Ninety-five percent of patients with mutations in IL2RG have lymphopenia, with total lymphocyte counts less than 2,000/mm 3 (normal 4,000-13,500/mm 3 ), based on clinical case series. All patients have very low or absent T cells, and approximately 88% have low or absent NK cells (5). Lymphopenia can be detected prenatally or after birth by obtaining a white cell count and differential; however subset analysis by flow cytometry is necessary to enumerate T, B and NK cells. Abnormal lymphocyte counts and analysis of T-cell function using in vitro responses of peripheral blood lymphocytes to phytomitogens and common antigens are currently used to diagnose this disorder (7). The diagnosis can be confirmed by sequence analysis of the IL2RG gene. Female carriers of IL2RG mutations can be identified by nonrandom X chromosome inactivation in lymphoid cells or by sequence analysis if the mutation is known. Prenatal diagnosis involves collection of fetal cells by amniocentesis or chorionic villus biopsy to look for known mutations or by fetal blood sampling to examine for lymphopenia, low T-cell counts, and poor T-cell blastogenic responses to mitogens (5).

**Population Testing**

Specific testing for SCID is currently done only on symptomatic individuals and in families with affected individuals. Some cases are also identified as a result of blood analysis performed for unrelated reasons. Although recent data shows that intervention shortly after birth (before the onset of symptoms) clearly improves outcome (1, 4), there is currently no program to detect infants with SCID. Testing for lymphopenia using a cord blood total lymphocyte count and a subset analysis using flow cytometry immediately after birth has been suggested, but the sensitivity and specificity has not been evaluated and thus may not be practical on a large scale. Detection of T-cell lymphopenia from the dried blood spots (DBS) currently collected from each newborn would allow the integration of SCID screening into the existing newborn screening system. If a DBS test could be developed and validated through large population pilot studies, it could potentially be incorporated into the current newborn screening programs.

**References**


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7. Primary Immunodeficiency Diseases. Report of an IUIS Committee. *Clinical Exp Immunol*. 1999;118 (suppl. 1):1-28.
8. National Human Genome Research Institute. X-linked SCID mutation database (no date provided). Accessed June 18, 2002

**Web Sites**

1. National Human Genome Research Institute. X-linked SCID mutation database
2. The SCID Homepage